IgG4-Related Gastrointestinal Lesion

21

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Introduction

IgG4-related disease has recently been recognized as a systemic condition that is characterized by increased serum IgG4 levels and responsiveness to steroid therapy. Patients with IgG4-RD show organ enlargement or nodular lesions with abundant lymphocyte and IgG4-positive plasma cell infiltration and fibrosis, and they frequently present both clinically and radiologically with findings suggestive of malignancy, which may result in unnecessary resection [1–3]. According to the comprehensive clinical diagnostic criteria for IgG4-RD [4], the diagnosis of IgG4-RD is made in the presence of a characteristic diffuse/localized swelling or mass in one or more organs with increased serum IgG4 levels or histological findings of abundant IgG4-positive plasma cell and lymphocyte infiltration associated with fibrosis.

Although there have been reports of infiltration of many IgG4-positive plasma cells in the gastric mucosa, colonic mucosa, and major duodenal papilla of some AIP patients [5–11], whether they are the lesions involved in IgG4-RD is unclear. This chapter reviews the published literature about the relationships between IgG4 and gastrointestinal diseases such as esophagitis, gastritis, colitis, and duodenal papillitis with abundant IgG4-positive plasma cell infiltration to clarify IgG4-related gastrointestinal disease.

IgG4-Related Esophageal Lesions

There have been two case reports of IgG4-related esophageal disease, which presented with dysphagia, weight loss, and recurrent esophageal strictures [12, 13]. On endoscopy, wall thickening was observed, and endoscopic ultrasound showed a submucosal lesion mass in one case. Since the possibility of malignancy and gastrointestinal stromal tumor could not be ruled out, esophageal resection was performed in both cases. Gross examination showed esophageal submucosal strictures with wall thickening. On histological examinations, transmural chronic fibrotic inflammation with abundant IgG4-positive plasma cell and lymphocyte infiltration and phlebitis were observed. The postoperative serum IgG4 level was 138 mg/dL in one case. Both cases showed no evidence of other IgG4-RD, including AIP, but they met the criteria of IgG4-RD. Thus, both cases were considered to show esophageal manifestations of IgG4-RD and could be called IgG4-related esophagitis. If unexplained esophageal stricture mimicking malignancy is seen, IgG4-related esophagitis must be considered in the differential diagnosis to avoid unnecessary surgery.

IgG4-Related Gastric Lesions

There have been nine cases in seven reports of IgG4-related gastric disease [14–20]. Seven cases were presented with abdominal symptoms like discomfort ($n=2$), abdominal pain ($n=1$), appetite loss ($n=1$), anorexia ($n=1$), weight loss ($n=1$), nausea ($n=1$), and vomiting ($n=1$). The other two cases found to have hard and fixed mass lesion in the stomach during upper endoscopy. Endoscopy findings showed submucosal tumor (SMT, $n=2$), refractory ulcer with stricture ($n=2$), and polypoid lesion ($n=4$). Endoscopic ultrasound with 2 cases showed lamina propria lesion mass. The serum IgG4 level was elevated in 2 of 4 cases. Because they could not deny the possibility of malignancy, the way of biopsy ($n=2$), endoscopic submucosal dissection ($n=1$), and resection ($n=6$) were performed. All 4 resected cases revealed dense infiltration of IgG4-positive plasma cell and marked submucosal fibrosis with storiform pattern.

Infiltration of many IgG4-positive plasma cells has been reported in the gastric mucosa of 33–47 % of AIP patients [10, 21]. After steroid therapy for AIP, most IgG4-positive plasma cells that had infiltration in the gastric mucosa disappeared

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[22]. However, these gastric lesions cannot be called IgG4-related gastric disease, because neither dense fibrosis nor obliterative phlebitis was seen in the gastric mucosa of AIP patients.

IgG4-Related Major Duodenal Papillary Lesions

There has been only one report of an IgG4-related pseudotumor of the major duodenal papilla [23]. On duodenoscopy, a red, irregular, penile-shaped mass was seen protruding from the submucosa. Suspecting an atypical submucosal neoplastic lesion, the patient underwent pylorus-preserving pancreaticoduodenectomy. On histology, a lymphoplasmacytic granuloma with abundant IgG4-positive plasma cells localized to the major duodenal papilla was seen. In this case, no other IgG4-RD including AIP was present.

It has been reported that the duodenal major papilla is swollen in 41–65 % of AIP patients [24–26]. Abundant IgG4-positive plasma cell infiltration is detected in 55–80 % of AIP patients [8, 10, 24, 25]. Both a swollen major papilla and abundant IgG4-positive plasma cell infiltration have improved following treatment with steroids [8, 27]. In the resected pancreas of AIP patients, lymphoplasmacytic inflammation with many IgG4-positive plasma cells was found in the major duodenal papilla attached to the head of the pancreas. Therefore, the papillary lesions that are frequently detected in AIP patients are not papillary manifestations of IgG4-related RD; they represent direct spread from inflammation of the pancreatic head, although biopsy of the major papilla and histological examination with IgG4 immunostaining are useful to support a diagnosis of AIP [8, 24, 25, 28, 29].

IgG4-Related Colonic Lesions

Matsui et al. [30] reported a case of an AIP patient with a colonic polyp containing many IgG4-positive plasma cells [31] who developed colonic polyposis with many IgG4-positive plasma cells 1 year after complete remission of AIP with steroid treatment. The polyposis was markedly reduced with re-administration of steroids. They suggested that the immunopathogenesis involved enhanced T-helper type 2 responses to intestinal microflora in patients with IgG4-RD [32]. Well-circumscribed sclerosing nodular lesions of the cecum and sigmoid colon composed of hyalinized fibrocollagenous tissue with abundant IgG4-positive plasma cell infiltration were reported, and the two cases had no other IgG4-RD [20]. These polypoid or nodular lesions appear to be IgG4-related colonic lesions.

Although infiltration of many IgG4-positive plasma cells is occasionally seen in the colonic mucosa of AIP patients, dense fibrosis or obliterative phlebitis was not observed in the lesion [1, 5–7, 11, 33, 34]. While Ravi et al. [35] have suggested the possibility that inflammatory bowel disease represents an extrapancreatic manifestation of AIP, in general, ulcerative colitis (UC) is rarely seen with type 1AIP [2, 36]. Although IgG4-positive plasma cell infiltration is sometimes detected in the colonic mucosa of UC patients [11, 37–39], the mechanisms underlying IgG4-positive plasma cell infiltration in the colonic mucosa of UC patients remain unknown. Mere infiltration of many IgG4-positive plasma cells in the colonic mucosa in AIP or UC patients does not appear to be considered a colonic lesion of IgG4-RD.

IgG4-Related Ileal Lesion

There are two reports about ileal lesions involved in IgG4-related disease.

One is an IgG4-related inflammatory pseudotumor of an ileal conduit. An ill-defined, fibrotic, tumor-like mass, histologically showing fibrosis with infiltration of lymphocytes and IgG4-positive plasma cells and marked obliterative phlebitis, occurred in an ileal conduit created as part of surgery for urinary bladder cancer [40].

The other case is an isolated, stenosing chronic ulcer in the jejunum associated with necrotizing mesenteric arteries. Abundant infiltration of IgG4-positive plasma cells was identified in the jejunal wall, mesenteric artery, and mesenteric lymph nodes [41].

Discussion

IgG4-RD shows organ enlargement or nodular lesions consisting of abundant lymphocyte and IgG4-positive plasma cell infiltration and fibrosis in various organs, either simultaneously or metachronously [2, 3]. The first International Symposium on IgG4-RD held in 2011 suggested that the term "IgG4-related disease" recognizes aptly the ubiquity of IgG4 within involved organs and proposed a style that uses "IgG4-related" as a prefix to the organ system affected, along with pathological guidelines for the diagnosis of RD [3, 42]. The diagnosis of IgG4-RD rests on the combined presence of the characteristic histopathological appearance and increased numbers of IgG4-positive plasma cells. On histological examination, highly suggested IgG4-RD requires the identification of at least two of three characteristic histological features including: (1) dense lymphoplasmacytic infiltration; (2) fibrosis, usually storiform in character; and (3) obliterative phlebitis. The IgG4 counts required for the diagnosis differ among affected organs, ranging from 10 to 200 cells/hpf. The diagnosis of IgG4-RD requires corroboration between histopathological findings and clinical information

such as elevated serum IgG4 levels, other organ involvement consistent with IgG4-RD, and effective response to treatment with steroids [42].

Infiltration of many IgG4-positive plasma cells is found in gastric and colonic mucosa and the major duodenal papilla of some AIP patients [1, 5–11, 21, 22, 24, 25, 33, 34]. However, since none of mass-like formation, dense fibrosis, or obliterative phlebitis was observed in these lesions, they cannot be diagnosed as gastrointestinal lesions involved in IgG4-RD. We consider both the clinical findings of mass formation and the histological findings of abundant infiltration of IgG4-positive plasma cells with fibrosis to be necessary when diagnosing IgG4-related gastrointestinal disease.

IgG4-related pseudotumors have been reported in several organs such as the liver and lung [43–45]. Based on a review of the literature, there appear to be two types in IgG4-related gastrointestinal disease. One is a gastrointestinal lesion showing marked thickening of the wall of the esophagus and stomach, consisting of dense fibrosis with abundant IgG4-positive plasma cell infiltration, which usually shows submucosal spreading. The other is an IgG4-related pseudotumor in the gastrointestinal region, such as the stomach, colon, and major duodenal papilla, that presents as a polypoid or mass-like lesion.

Most solitary IgG4-related gastrointestinal lesions that are not associated with other IgG4-RD appear to be difficult to diagnose. It is vitally important to rule out malignancy. However, these lesions may respond to steroid therapy. To avoid unnecessary resection, the differential diagnosis must include IgG4-related gastrointestinal diseases.

Conclusions

In conclusion, IgG4-related gastrointestinal disease may be part of IgG4-RD. However, this remains unclear due to its rarity, and further study is needed. Therefore, in patients with unexplained thickening or SMT, pseudotumor, nodule, polyp, ulcer, or swelling, IgG4-related gastrointestinal disease should be considered in the differential diagnosis by both clinicians and pathologists to avoid unnecessary surgery and provide appropriate treatment.

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